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(54) **Medicaments for the treatment of urinary tract disorders comprising anticholinergic agents**

(57) The present invention relates to a the use of one or more, preferably one long acting anticholinergic for the preparation of a medicament for the treatment of urinary tract disorders.

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Description

[0001] The present invention relates to a the use of one or more, preferably one long acting anticholinergic for the preparation of a medicament for the treatment of urinary tract disorders.

Background of the invention:

[0002] Urinary tract disorders as for instance urinary incontinence (UI) caused by e.g. unstable detrusor /detrusor instability causes significant morbidity in sufferers and a great financial expense to health care providers. The condition is associated with symptoms of increased urinary frequency, urgency and urge incontinence. The embarrassing nature of these symptoms means patients are often reluctant to seek medical help and as a consequence there is under-reporting. Prevalence of UI is up to 30-40 % in male and female patients.

[0003] The present invention targets these receptors by administration of long acting anticholinergic agents via various routes of administration to attain prolonged maintenance of bladder control in otherwise incontinent patients. Furthermore, it is the object of the present invention to provide for alternative, advantageous methods for the treatment of urinary tract disorders, as for instance urinary incontinence.

Description of the invention

[0004] The present invention relates to the use of one or more, preferably one long acting anticholinergic 1 for the preparation of a medicament for the treatment of urinary tract disorders.

[0005] The term "long acting anticholinergic" defines anticholinergic agents that show a long duration of action. These long acting anticholinergics show a pharmacokinetic profile that allows administration once or twice, preferably once per day.

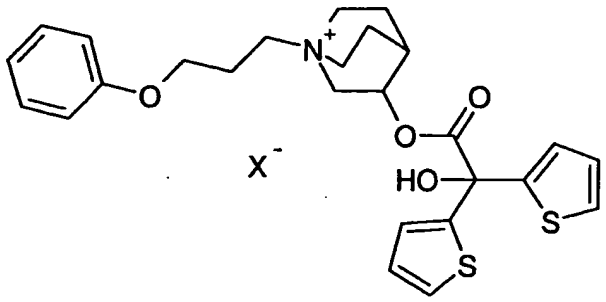
[0006] Preferably, the present invention relates to the use of one or more, preferably one long acting anticholinergic 1 for the preparation of a medicament for the treatment of urinary tract disorders selected from among urinary incontinence, urge urinary incontinence, stress urinary incontinence, mixed urinary incontinence, spasms of the urinary tract, urolithiasis, urinary tract cysts, urinary tract polyps, preparation for diagnostic and curative interventions in the urinary tract. More preferably, the present invention relates to the use of one or more, preferably one long acting anticholinergic 1 for the preparation of a medicament for the treatment of urinary tract disorders selected from among urinary incontinence, urge urinary incontinence, stress urinary incontinence, mixed urinary incontinence and urolithiasis. Preferably, the present invention relates to the use of one or more, preferably one long acting anticholinergic 1 for the preparation of a medicament for the treatment of urinary tract disorders selected from among urinary incontinence, urge urinary incontinence, stress urinary incontinence and mixed urinary incontinence.

[0007] In a preferred embodiment the invention relates to the use of one or more, preferably one long acting anticholinergic 1 for the preparation of a medicament for the treatment of the urinary tract disorders mentioned hereinbefore, wherein the long acting anticholinergic 1 is selected from among tiotropium salts, glycopyrronium salts and trospium salts. In the above-mentioned salts the cations tiotropium, glycopyrronium and trospium are the pharmacologically active components. Within the scope of the present patent application, an explicit reference to the above cations is indicated by the use of the number 1'. Any reference to the aforementioned salts 1 naturally also includes a reference to the ingredients 1' (tiotropium, glycopyrronium or trospium). Glycopyrronium salts are preferably used in their enantiomerically pure form. From the various diastereomers known for glycopyrronium salts the R,R-glycopyrronium salts are of outstanding importance. By the salts 1 which may be used within the scope of the present invention are meant the compounds which contain, in addition to tiotropium, glycopyrronium or trospium as counter-ion (anion), chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate or p-toluenesulphonate, wherein chloride, bromide, iodide, sulphate, methanesulphonate or para-toluenesulphonate are preferred. Within the scope of the present invention, the methanesulphonate, chloride, bromide and iodide are preferred of all the salts 1. If trospium salts are used the chloride is of particular importance. From the other salts mentioned hereinbefore the methanesulphonate and bromide are of particular importance. Of particular importance according to the invention are salts 1 selected from among enantiomerically pure glycopyrronium salts and tiotropium salts. In the use according to the invention tiotropium bromide is particularly preferred. The aforementioned salts may be optionally present in form of their solvates or hydrates, preferably in form of their hydrates. If tiotropium bromide is used it is preferably present in form of its crystalline tiotropium bromide monohydrate as disclosed in WO 02/30928. In case tiotropium bromide is used in anhydrous form, it is preferably present in form of the crystalline tiotropium bromide anhydrate disclosed in WO 03/000265.

[0008] Optionally the long acting anticholinergic agents mentioned hereinbefore possess chiral carbon centers. In this case the pharmaceutical compositions according to the invention may contain the long acting anticholinergic agents in form of their enantiomers, mixtures of enantiomers or racemats. Preferably chiral long acting anticholinergics are present

in form of one of their pure enantiomers.

[0009] In another preferred embodiment the invention relates to the use of one or more, preferably one long acting anticholinergic 1 for the preparation of a medicament for the treatment of the urinary tract disorders mentioned hereinbefore, wherein the long acting anticholinergic 1 is selected from among the salts of LAS 34273, being characterized by the formula 1a



1a

wherein

X - denotes an anion with a single negative charge, preferably an anion selected from the group consisting of fluoride, chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate and p-toluenesulphonate,

optionally in the form of the racemates, the enantiomers, and the hydrates thereof.

[0010] Within the use according to the invention, preferably the salts of formula 1a are used wherein

X - denotes an anion with a single negative charge selected from among the fluoride, chloride, bromide, 4-toluenesulphonate and methanesulphonate, preferably bromide,

optionally in the form of the racemates, the enantiomers, and the hydrates thereof.

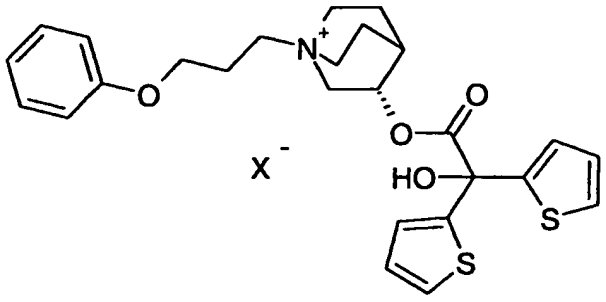
[0011] More preferably, the salts of formula 1a are used wherein

X^- denotes an anion with a single negative charge selected from among the chloride, bromide and methanesulphonate, preferably bromide,

optionally in the form of the racemates, the enantiomers, and the hydrates thereof.

[0012] Particularly preferred according to the invention is the salt of formula 1a wherein X^- denotes bromide.

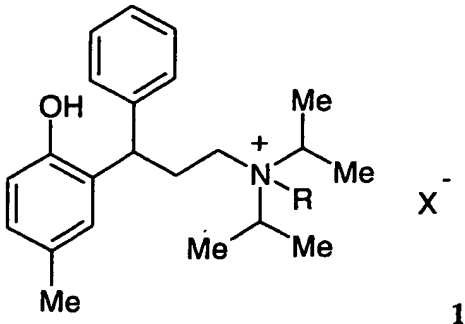
[0013] Of particular interest in the use according to the invention are the enantiomers of formula 1a-en



1a-en

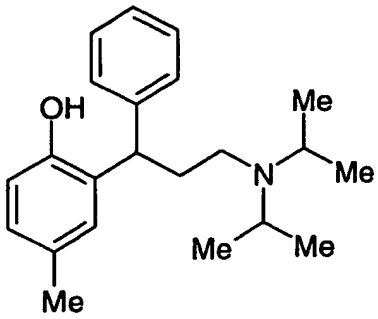
wherein X^- may have the meanings as mentioned hereinbefore.

[0014] In another preferred embodiment the invention relates to the use of one or more, preferably one long acting anticholinergic 1 for the preparation of a medicament for the treatment of the urinary tract disorders mentioned hereinbefore, wherein the long acting anticholinergic 1 is selected from the compounds of formula 1b



1b

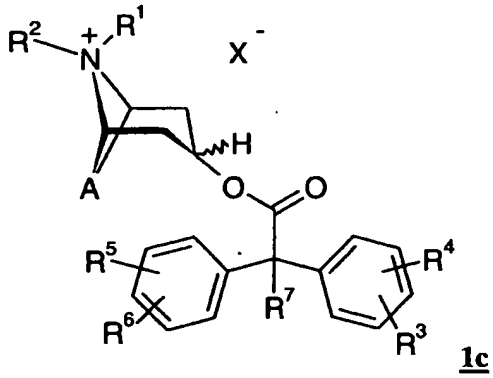
wherein R is either methyl or ethyl and wherein X^- may have the meanings as mentioned hereinbefore. In the alternative the compound according to formula **1b** may be present in form of its free base according to formula **1b-base**



1b-base.

[0015] In the use according to the invention the long acting anticholinergic agents of formula **1b** (or **1b-base**) may be applied in form of their enantiomers, mixtures of enantiomers or racemats. Preferably, the long acting anticholinergic agent of formula **1b** (or **1b-base**) is applied in form of its R-enantiomer.

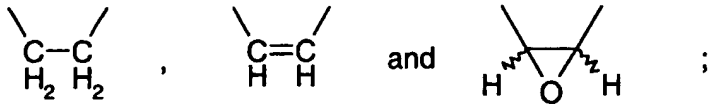
[0016] In another preferred embodiment the invention relates to the use of one or more, preferably one long acting anticholinergic **1** for the preparation of a medicament for the treatment of the urinary tract disorders mentioned hereinbefore, wherein the long acting anticholinergic **1** is selected from the compounds of formula **1c**



1c

wherein

A denotes a double-bonded group selected from among



X^-	may have the meanings as mentioned hereinbefore, preferably chloride, bromide or methansulphonate,
R^1 and R^2	which may be identical or different denote a group selected from among methyl, ethyl, n-propyl and iso-propyl, which may optionally be substituted by hydroxy or fluorine, preferably unsubstituted methyl;
R^3, R^4, R^5 and R^6,	which may be identical or different, denote hydrogen, methyl, ethyl, methyloxy, ethyloxy, hydroxy, fluorine, chlorine, bromine, CN, CF_3 or NO_2;
R^7	denotes hydrogen, methyl, ethyl, methyloxy, ethyloxy, $-CH_2-F$, $-CH_2-CH_2-F$, $-O-CH_2-F$, $-O-CH_2-CH_2-F$, $-CH_2-OH$, $-CH_2-CH_2-OH$, CF_3, $-CH_2-OMe$, $-CH_2-CH_2-OMe$, $-CH_2-OEt$, $-CH_2-CH_2-OEt$, -O-COMe, -O-COEt, $-O-COCF_3$, $-O-COCF_3$, fluorine, chlorine or bromine.

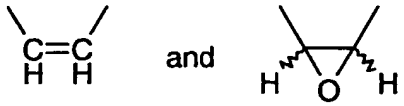
[0017] The compounds of formula **1c** are known in the art (WO 02/32899).

[0018] In a preferred embodiment of the invention the compounds of formula **1c** are used, wherein

X^-	denotes bromide;
R^1 and R^2	which may be identical or different denote a group selected from methyl and ethyl, preferably methyl;
R^3, R^4, R^5 and R^6,	which may be identical or different, denote hydrogen, methyl, methyloxy, chlorine or fluorine;
R^7	denotes hydrogen, methyl or fluorine.

[0019] Of particular importance within the use according to the invention are compounds of general formula **1c**, wherein

A denotes a double-bonded group selected from among

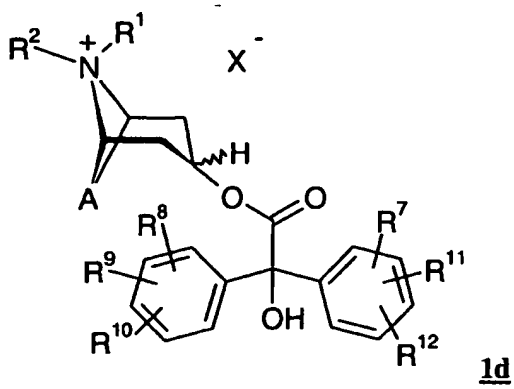


[0020] The compounds of formula **1c**, may optionally be administered in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates thereof.

[0021] Of particular importance for the use according to the invention are the following compounds of formula **1c**:

- tropenol 2,2-diphenylpropionic acid ester methobromide,
- scopine 2,2-diphenylpropionic acid ester methobromide,
- scopine 2-fluoro-2,2-diphenylacetic acid ester methobromide and
- tropenol 2-fluoro-2,2-diphenylacetic acid ester methobromide.

[0022] In a yet another preferred embodiment the invention relates to the use of one or more, preferably one long acting anticholinergic **1** for the preparation of a medicament for the treatment of the urinary tract disorders mentioned hereinbefore, wherein the long acting anticholinergic **1** is selected from the compounds of formula **1d**



1d

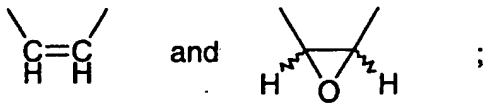
wherein

A, X -, R^1 and R^2	may have the meanings as mentioned hereinbefore and wherein
R^7, R^8, R^9, R^{10}, R^{11} and R^{12},	which may be identical or different, denote hydrogen, methyl, ethyl, methyloxy, ethyloxy, hydroxy, fluorine, chlorine, bromine, CN, CF_3 or NO_2, with the proviso that at least one of the groups R^7, R^8, R^9, R^{10}, R^{11} and R^{12} is not hydrogen.

[0023] The compounds of formula 1d are known in the art (WO 02/32898).

[0024] In a preferred embodiment the invention relates to the aforementioned use of compounds of formula 1d, wherein

A	denotes a double-bonded group selected from among



;

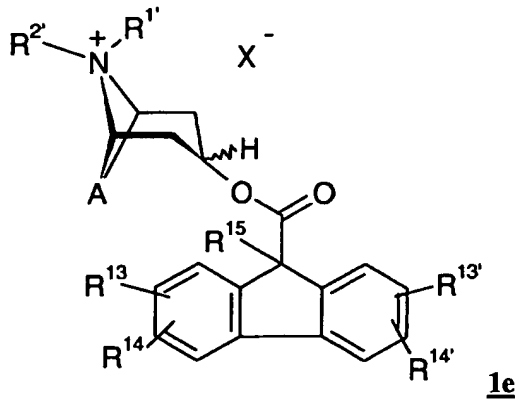
X^-	denotes bromide;
R^1 and R^2	which may be identical or different denote methyl or ethyl, preferably methyl;
R^7, R^8, R^9, R^{10}, R^{11} and R^{12},	which may be identical or different, denote hydrogen, fluorine, chlorine or bromine, preferably fluorine with the proviso that at least one of the groups R^7, R^8, R^9, R^{10}, R^{11} and R^{12} not hydrogen.

[0025] Of particular importance within the use according to the invention are the following compounds of formula 1d:

- tropenol 3,3',4,4'-tetrafluorobenzilic acid ester methobromide,
- scopine 3,3',4,4'-tetrafluorobenzilic acid ester methobromide,
- scopine 4,4'-difluorobenzilic acid ester methobromide,
- tropenol 4,4'-difluorobenzilic acid ester methobromide,
- scopine 3,3'-difluorobenzilic acid ester methobromide, and
- tropenol 3,3'-difluorobenzilic acid ester methobromide.

[0026] The pharmaceutical compositions according to the invention may contain the compounds of formula 1d optionally in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates thereof.

[0027] In a yet another preferred embodiment the invention relates to the use of one or more, preferably one long acting anticholinergic 1 for the preparation of a medicament for the treatment of the urinary tract disorders mentioned hereinbefore, wherein the long acting anticholinergic 1 is selected from the compounds of formula 1e



1e

wherein A and X - may have the meanings as mentioned hereinbefore, and wherein

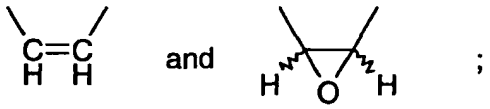
R^{15}	denotes hydrogen, hydroxy, methyl, ethyl, $-CF_3$, CHF_2 or fluorine;
$R^{1'}$ and $R^{2'}$	which may be identical or different denote C_1-C_5-alkyl which may optionally be substituted by C_3-C_6-cycloalkyl, hydroxy or halogen, or $R^{1'}$ and $R^{2'}$ together denote a $-C_3$-C_5-alkylene-bridge;
R^{13}, R^{14}, $R^{13'}$ and $R^{14'}$	which may be identical or different denote hydrogen, $-C_1$-C_4-alkyl, $-C_1$-C_4-alkyloxy, hydroxy, $-CF_3$, $-CHF_2$, CN, NO_2 or halogen,

optionally together with a pharmaceutically acceptable excipient.

[0028] The compounds of formula **1e** are known in the art (WO 03/064419).

[0029] In a preferred embodiment the invention relates to the aforementioned use of compounds of formula **1e**, wherein

A	denotes a double-bonded group selected from among

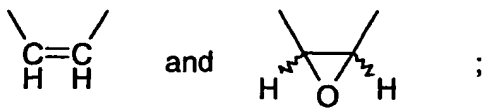


;

X^-	denotes an anion selected from among chloride, bromide and methanesulphonate, preferably bromide;
R^{15}	denotes hydroxy, methyl or fluorine, preferably methyl or hydroxy;
$R^{1'}$ and $R^{2'}$	which may be identical or different represent methyl or ethyl, preferably methyl;
R^{13}, R^{14}, $R^{13'}$ and $R^{14'}$	which may be identical or different represent hydrogen, $-CF_3$, $-CHF_2$ or fluorine, preferably hydrogen or fluorine.

[0030] In another preferred embodiment the invention relates to the aforementioned use of compounds of formula **1e**, wherein

A	denotes a double-bonded group selected from among



;

X^-	denotes bromide;
R^{15}	denotes hydroxy or methyl, preferably methyl;
$R^{1'}$ and $R^{2'}$	which may be identical or different represent methyl or ethyl, preferably methyl;

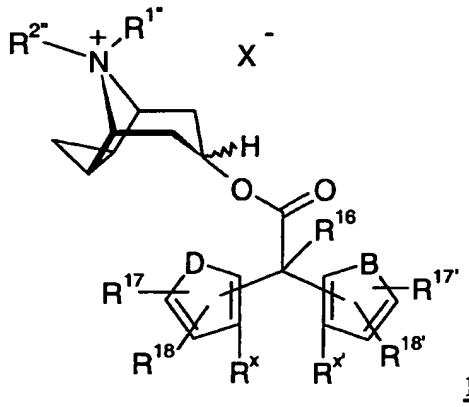
R^{13}, R^{14}, $R^{13'}$ and $R^{14'}$ which may be identical or different represent hydrogen or fluorine.

[0031] Of particular importance within the use according to the invention are the following compounds of formula **1e**:

- tropenol 9-hydroxy-fluorene-9-carboxylate methobromide ;
- tropenol 9-fluoro-fluorene-9-carboxylate methobromide ;
- scopine 9-hydroxy-fluorene-9-carboxylate methobromide ;
- scopine 9-fluoro-fluorene-9-carboxylate methobromide ;
- tropenol 9-methyl-fluorene-9-carboxylate methobromide ;
- scopine 9-methyl-fluorene-9-carboxylate methobromide .

[0032] The pharmaceutical compositions according to the invention may contain the compounds of formula **1e** optionally in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates thereof.

[0033] In a yet another preferred embodiment the invention relates to the use of one or more, preferably one long acting anticholinergic **1** for the preparation of a medicament for the treatment of the urinary tract disorders mentioned hereinbefore, wherein the long acting anticholinergic **1** is selected from the compounds of formula **1f**



1f

wherein X - may have the meanings as mentioned hereinbefore, and wherein

D and B	which may be identical or different, preferably identical, denote -O, -S, -NH, $-CH_2$, -CH=CH, or $-N(C_1-C_4\text{-alkyl})$-;
R^{16}	denotes hydrogen, hydroxy, $-C_1-C_4$-alkyl, $-C_1-C_4$-alkyloxy, $-C_1-C_4$-alkylene-Halogen, $-O-C_1-C_4$-alkylene-halogen, $-C_1-C_4$-alkylene-OH, $-CF_3$, CHF_2, $-C_1-C_4$-alkylene-C_1-C_4-alkyloxy, $-O-COC_1-C_4$-alkyl, $-O-COC_1-C_4$-alkylene-halogen, $-C_1-C_4$-alkylene-C_3-C_6-cycloalkyl, $-O-COCF_3$ or halogen;
R^{1*} and R^{2*}	which may be identical or different, denote $-C_1-C_5$-alkyl, which may optionally be substituted by $-C_3-C_6$-cycloalkyl, hydroxy or halogen, or R^{1*} and R^{2*} together denote a $-C_3-C_5$-alkylene bridge;
R^{17}, R^{18}, $R^{17'}$ and $R^{18'}$,	which may be identical or different, denote hydrogen, C_1-C_4-alkyl, C_1-C_4-alkyloxy, hydroxy, $-CF_3$, $-CHF_2$, CN, NO_2 or halogen;
R^x and $R^{x'}$	which may be identical or different, denote hydrogen, C_1-C_4-alkyl, C_1-C_4-alkyloxy, hydroxy, $-CF_3$, $-CBF_2$, CN, NO_2 or halogen or R^x and $R^{x'}$ together denote a single bond or a bridging group selected from among the bridges -O, -S, -NH, $-CH_2$, $-CH_2-CH_2$-, $-N(C_1-C_4\text{-alkyl})$, $-CH(C_1-C_4\text{-alkyl})$- and $-C(C_1-C_4\text{-alkyl})_2$.

[0034] The compounds of formula **1f** are known in the art (WO 03/064418).

[0035] In another preferred embodiment the invention relates to the use of compounds of formula **1f** wherein

X^-	denotes chloride, bromide, or methanesulphonate, preferably bromide;
D and B	which may be identical or different, preferably identical, denote -O, -S, -NH or -CH=CH-;
R^{16}	denotes hydrogen, hydroxy, $-C_1-C_4$-alkyl, $-C_1-C_4$-alkyloxy, $-CF_3$, $-CBF_2$, fluorine, chlorine or

	bromine;
$R^{1''}$ and $R^{2''}$	which may be identical or different, denote C_1-C_4-alkyl, which may optionally be substituted by hydroxy, fluorine, chlorine or bromine, or $R^{1''}$ and $R^{2''}$ together denote a -C_3-C_4-alkylene-bridge;
R^{17}, R^{18}, $R^{17'}$ and $R^{18'}$,	which may be identical or different, denote hydrogen, C1-C4-alkyl, C1-C4-alkyloxy, hydroxy, -CF3, -CHF2, CN, NO2, fluorine, chlorine or bromine;
R^x and $R^{x'}$	which may be identical or different, denote hydrogen, C_1-C_4-alkyl, C_1-C_4-alkyloxy, hydroxy, -CF_3, -CEF_2, CN, NO_2, fluorine, chlorine or bromine or R^X and $R^{X'}$ together denote a single bond or a bridging group selected from among the bridges -O, -S, -NH- and -CH_2-.

[0036] In another preferred embodiment the invention relates to the aforementioned use of compounds of formula **1f**, wherein

X^-	denotes chloride, bromide, or methanesulphonate, preferably bromide;
D and B	which may be identical or different, preferably identical, denote -S or -CH=CH-;
R^{16}	denotes hydrogen, hydroxy or methyl;
$R^{1''}$ and $R^{2''}$	which may be identical or different, denote methyl or ethyl;
R^{17}, R^{18}, $R^{17'}$ and $R^{18'}$,	which may be identical or different, denote hydrogen, -CF_3 or fluorine, preferably hydrogen;
R^x and $R^{x'}$	which may be identical or different, denote hydrogen, -CF_3 or fluorine, preferably hydrogen or R^x and $R^{x'}$ together denote a single bond or the bridging group -O-.

[0037] In another preferred embodiment the invention relates to the aforementioned use of compounds of formula **1f**, wherein

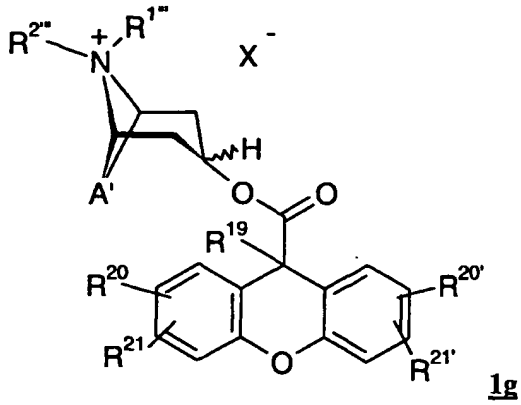
X^-	denotes bromide;
D and B	denote -CH=CH-;
R^{16}	denotes hydrogen, hydroxy or methyl;
$R^{1''}$ and $R^{2''}$	denote methyl;
R^{17}, R^{18}, $R^{17'}$ and $R^{18'}$,	which may be identical or different, denote hydrogen or fluorine, preferably hydrogen;
R^x and $R^{X'}$	which may be identical or different, denote hydrogen or fluorine, preferably hydrogen or R^X and $R^{X'}$ together denote a single bond or the bridging group -O-.

[0038] Of particular importance within the use according to the invention are the following compounds of formula **1f**:

- cyclopropyltropine benzilate methobromide;
- cyclopropyltropine 2,2-diphenylpropionate methobromide;
- cyclopropyltropine 9-hydroxy-xanthene-9-carboxylate methobromide;
- cyclopropyltropine 9-methyl-fluorene-9-carboxylate methobromide;
- cyclopropyltropine 9-methyl-xanthene-9-carboxylate methobromide;
- cyclopropyltropine 9-hydroxy-fluorene-9-carboxylate methobromide ;
- cyclopropyltropine methyl 4,4'-difluorobenzilate methobromide.

[0039] The pharmaceutical compositions according to the invention may contain the compounds of formula **1f** optionally in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates thereof.

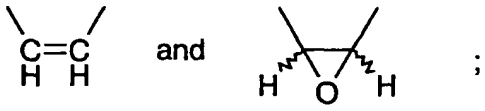
[0040] In a yet another preferred embodiment the invention relates to the use of one or more, preferably one long acting anticholinergic **1** for the preparation of a medicament for the treatment of the urinary tract disorders mentioned hereinbefore, wherein the long acting anticholinergic **1** is selected from the compounds of formula **1g**



1g

wherein X^- may have the meanings as mentioned hereinbefore, and wherein

A' denotes a double-bonded group selected from among



;

R^{19} denotes hydroxy, methyl, hydroxymethyl, ethyl, $-CF_3$, CHF_2 or fluorine;

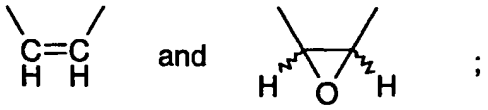
$R^{1'''}$ and $R^{2'''}$ which may be identical or different denote C_1-C_5-alkyl which may optionally be substituted by C_3-C_6-cycloalkyl, hydroxy or halogen, or $R^{1'''}$ and $R^{2'''}$ together denote a $-C_3$-C_5-alkylene-bridge;

R^{20}, R^{21}, $R^{20'}$ and $R^{21'}$ which may be identical or different denote hydrogen, $-C_1$-C_4-alkyl, $-C_1$-C_4-alkyloxy, hydroxy, $-CF_3$, $-CBF_2$, CN, NO_2 or halogen.

[0041] The compounds of formula 1g are known in the art (WO 03/064417).

[0042] In another preferred embodiment the invention relates to the aforementioned use of compounds of formula 1g wherein

A' denotes a double-bonded group selected from among



;

X^- denotes chloride, bromide or methanesulphonate, preferably bromide;

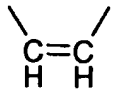
R^{19} denotes hydroxy or methyl;

$R^{1'''}$ and $R^{2'''}$ which may be identical or different represent methyl or ethyl, preferably methyl;

R^{20}, R^{21}, $R^{20'}$ and $R^{21'}$ which may be identical or different represent hydrogen, $-CF_3$, - CHF_2 or fluorine, preferably hydrogen or fluorine.

[0043] In another preferred embodiment the invention relates to the aforementioned use of compounds of formula 1g wherein

A' denotes a double-bonded group selected from among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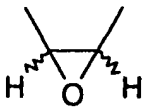

;

X^-	denotes bromide;
R^{19}	denotes hydroxy or methyl, preferably methyl;
$R^{1'''}$ and $R^{2'''}$	which may be identical or different represent methyl or ethyl, preferably methyl;
R^3, R^4, $R^{3'}$ and $R^{4'}$	which may be identical or different represent hydrogen or fluorine.

[0044] Of particular importance within the use according to the invention are the following compounds of formula **1g**:

- tropenol 9-hydroxy-xanthene-9-carboxylate methobromide ;
- scopine 9-hydroxy-xanthene-9-carboxylate methobromide ;
- tropenol 9-methyl-xanthene-9-carboxylate methobromide ;
- scopine 9-methyl-xanthene-9-carboxylate methobromide ;
- tropenol 9-ethyl-xanthene-9-carboxylate methobromide ;
- tropenol 9-difluoromethyl-xanthene-9-carboxylate methobromide ;
- scopine 9-hydroxymethyl-xanthene-9-carboxylate methobromide .

[0045] The pharmaceutical compositions according to the invention may contain the compounds of formula **1g** optionally in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates thereof.

[0046] The alkyl groups used, unless otherwise stated, are branched and unbranched alkyl groups having 1 to 5 carbon atoms. Examples include: methyl, ethyl, propyl or butyl. The groups methyl, ethyl, propyl or butyl may optionally also be referred to by the abbreviations Me, Et, Prop or Bu. Unless otherwise stated, the definitions propyl and butyl also include all possible isomeric forms of the groups in question. Thus, for example, propyl includes n-propyl and iso-propyl, butyl includes iso-butyl, sec. butyl and tert.-butyl, etc.

[0047] The cycloalkyl groups used, unless otherwise stated, are alicyclic groups with 3 to 6 carbon atoms. These are the cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups. According to the invention cyclopropyl is of particular importance within the scope of the present invention.

[0048] The alkylene groups used, unless otherwise stated, are branched and unbranched double-bonded alkyl bridges with 1 to 5 carbon atoms. Examples include: methylene, ethylene, propylene or butylene.

[0049] The alkylene-halogen groups used, unless otherwise stated, are branched and unbranched double-bonded alkyl bridges with 1 to 4 carbon atoms which may be mono-, di- or trisubstituted, preferably disubstituted, by a halogen. Accordingly, unless otherwise stated, the term alkylene-OH groups denotes branched and unbranched double-bonded alkyl bridges with 1 to 4 carbon atoms which may be mono-, di- or trisubstituted, preferably monosubstituted, by a hydroxy.

[0050] The alkyloxy groups used, unless otherwise stated, are branched and unbranched alkyl groups with 1 to 5 carbon atoms which are linked via an oxygen atom. The following may be mentioned, for example: methyloxy, ethyloxy, propyloxy or butyloxy. The groups methyloxy, ethyloxy, propyloxy or butyloxy may optionally also be referred to by the abbreviations MeO, EtO, PropO or BuO. Unless otherwise stated, the definitions propyloxy and butyloxy also include all possible isomeric forms of the groups in question. Thus, for example, propyloxy includes n-propyloxy and iso-propyloxy, butyloxy includes iso-butyloxy, sec. butyloxy and tert.-butyloxy, etc. The word alkoxy may also possibly be used within the scope of the present invention instead of the word alkyloxy. The groups methyloxy, ethyloxy, propyloxy or butyloxy may optionally also be referred to as methoxy, ethoxy, propoxy or butoxy.

[0051] The alkylene-alkyloxy groups used, unless otherwise stated, are branched and unbranched double-bonded alkyl bridges with 1 to 5 carbon atoms which may be mono-, di- or trisubstituted, preferably monosubstituted, by an alkyloxy group.

[0052] The -O-CO-alkyl groups used, unless otherwise stated, are branched and unbranched alkyl groups with 1 to 4 carbon atoms which are bonded via an ester group. The alkyl groups are bonded directly to the carbonylcarbon of the ester group. The term -O-CO-alkyl-halogen group should be understood analogously. The group -O-CO-CF_3 denotes trifluoroacetate.

[0053] Within the scope of the present invention halogen denotes fluorine, chlorine, bromine or iodine. Unless otherwise stated, fluorine and bromine are the preferred halogens. The group CO denotes a carbonyl group.

[0054] In another preferred embodiment the invention relates to a method for the treatment of urinary tract disorders as mentioned hereinbefore comprising the administrationm of a therapeutically effective amount of one or more, preferably one long acting anticholinergic **1**. The term "therapeutically effective amount" shall mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being

sought by a researcher or clinician.

[0055] Within the use of the present invention, the long acting anticholinergic 1 may be administered by oral, parenteral (e.g., intramuscular,intraperitoneal, intravenous or subcutaneous injection, or implant), buccal, nasal, vaginal, rectal, sublingual, topical (e.a.. ocular eyedrop) or inhalative routes of administration and may be formulated in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration.

[0056] The pharmaceutical compositions for the administration of the long acting anticholinergics 1 of this invention may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which is constituted of one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredients into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired dosage form. In the pharmaceutical compositions the active compounds are included in an amount sufficient to produce the desired pharmacologic effect.

[0057] The pharmaceutical compositions containing the active ingredients 1 that are suitable for oral administration may be in the form of discrete units such as hard or soft capsules, tablets, troches or lozenges, each containing a predetermined amount of the active ingredients; in the form of a dispersible powder or granules; in the form of a solution or a suspension in an aqueous liquid or non-aqueous liquid; in the form of syrups or elixirs; or in the form of an oil-in-water emulsion or a water-in-oil emulsion.

[0058] Dosage forms intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical formulations and such compositions.

[0059] The excipients used may be for example, (a) inert diluents such as mannitol, sorbitol, calcium carbonate, pregelatinized starch, lactose, calcium phosphate or sodium phosphate; (b) granulating and disintegrating agents, such as povidone, copovidone, hydroxypropylmethylcellulose, corn starch, alginic acid, crospovidone, sodiumstarchglycolate, croscarmellose, or polacrilin potassium ; (c) binding agents such as microcrystalline cellulose or acacia ; and (d) lubricating agents such as magnesium stearate, stearic acid, fumaric acid or talc.

[0060] In some cases, formulations for oral use may be in the form of hardgelatin or HPMC capsules wherein the active ingredient 1 is mixed with an inert solid diluent, for example pregelatinized starch, calcium carbonate, calcium phosphate or kaolin, or dispensed via a pellet formulation. They may also be in the form of soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, medium chain triglycerides or olive oil.

[0061] The tablets, capsules or pellets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a delayed action or sustained action over a longer period. For example, a time delay material such as celluloseacetate phtalate or hydroxypropylcellulose acetate succinate or sustained release material such as ethylcellulose or ammoniomethacrylate copolymer (type B) may be employed.

[0062] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions can also include adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, perfuming and preserving agents.

[0063] Aqueous suspensions normally contain the active ingredient 1 in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients may be (a) suspending agents such as hydroxy ethylcellulose, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; (b) dispersing or wetting agents which may be (b.1) a naturally-occurring phosphatide such as lecithin, (b.2) a condensation product of an alkylene oxide with a fatty acid, for example, polyoxyethylene stearate, (b.3) a condensation product of ethylene oxide with a long chain aliphatic alcohol, for example heptadecaethyleneoxycetanol, (b.4) a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol such as polyoxyethylene sorbitol monooleate, or (b.5) a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride, for example polyoxyethylene sorbitan monooleate.

[0064] The aqueous suspensions may also contain one or more preservatives, for example, ethyl or n-propyl p-hydroxybenzoate; one or more coloring agents; one or more flavoring agents; and one or more sweetening agents, such as sucrose or saccharin.

[0065] Oily suspensions may be formulated by suspending the active ingredients 1 in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents and flavoring agents may be added to provide a palatable oral preparation. These compositions may be prepared by the addition of an antioxidant such as ascorbic acid.

[0066] Dispersible powders and granules are suitable for the preparation of an aqueous suspension. They provide the active ingredients 1 in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives.

Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, those sweetening, flavoring and coloring agents described above may also be present.

[0067] The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil such as olive oil or arachis oils, or a mineral oil such as liquid paraffin or a mixture thereof.

[0068] Suitable emulsifying agents may be (a) naturally-occurring gums such as gum acacia and gum tragacanth, (b) naturally-occurring phosphatides such as soybean and lecithin, (c) esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan monooleate, (d) condensation products of said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

[0069] Syrups and elixirs may be formulated with sweetening agents, for example, glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a preservative and flavoring and coloring agents.

[0070] The pharmaceutical compositions containing 1 may be in the form of a sterile injectable aqueous or oleagenous suspension or solution. The suspension may be formulated according to known methods using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane-diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[0071] Preparations according to this invention containing 1 for parenteral administration include sterile aqueous or non-aqueous solutions, suspension, or emulsions.

[0072] Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized by, for example, filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile solid compositions which can be reconstituted in sterile water, or some other sterile injectable medium immediately before use. The combination of this invention may also be administered in the form of suppositories for rectal administration. This composition can be prepared by mixing the drugs with a suitable nonirritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter, hard fat, and polyethylene glycols. Compositions for buccal, nasal or sublingual administration are also prepared with standard excipients well known in the art.

[0073] For topical administration the compositions according to this invention containing 1 may be formulated in liquid or semi-liquid preparations such as liniments, lotions, applications; oil-in-water or water-in-oil emulsions such as creams, ointments, jellies or pastes, including tooth-pastes; or solutions or suspensions such as drops, and the like.

[0074] The dosage of the active ingredients in the compositions of this invention may be varied. However, it is necessary that the amount of the active ingredients 1 be such that a suitable dosage form is obtained. The selected dosage and the dosage form depend upon the desired therapeutic effect, on the route of administration and on the duration of the treatment. Dosage ranges in the combination are approximately one tenth to one times the clinically effective ranges required to induce the desired therapeutic effect, respectively when the compounds are used singly.

[0075] In a yet another prefered embodiment the invention relates to the pharmaceutical compositions mentioned hereinbefore.

[0076] Within the use according to the invention the long acting anticholinergics 1 may also be administered by inhalation. Inhalable preparations according to the invention include inhalable powders, propellant-containing metered dose aerosols or propellant-free inhalable solutions. Inhalable powders according to the invention containing the active substances may consist of the active substances on their own or of a mixture of the active substances with physiologically acceptable excipients. Within the scope of the present invention, the term carrier may optionally be used instead of the term excipient. Within the scope of the present invention, the term propellant-free inhalable solutions also includes concentrates or sterile inhalable solutions ready for use.

[0077] Inhalable powders may contain 1 either alone or in admixture with suitable physiologically acceptable excipients. If the active substance 1 is present in admixture with physiologically acceptable excipients, the following physiologically acceptable excipients may be used to prepare these inhalable powders according to the invention: monosaccharides (e.g. glucose or arabinose), disaccharides (e.g. lactose, saccharose, maltose, trehalose), oligo- and polysaccharides (e.g. dextran), polyalcohols (e.g. sorbitol, mannitol, xylitol), cyclodextrines (e.g. α-cyclodextrine, β-cyclodextrine, χ-cyclodextrine, methyl-β-cyclodextrine, hydroxypropyl-β-cyclodextrine), salts (e.g. sodium chloride, calcium carbonate) or mixtures of these excipients with one another. Preferably, mono- or disaccharides are used, while the use of lactose, trehalose or glucose is preferred, particularly, but not exclusively, in the form of their hydrates.

[0078] Inhalable powders preferably contain excipients with a maximum average particle size of up to 250μm, pref-

erably between 10 and 150μm, most preferably between 15 and 80μm. It may sometimes seem appropriate to add finer excipient fractions with an average particle size of 1 to 9μm to the excipient mentioned above. These finer excipients are also selected from the group of possible excipients listed hereinbefore. Finally, in order to prepare the inhalable powders according to the invention, micronised active substance, preferably with an average particle size of 0.5 to 10μm, more preferably from 1 to 6μm, is added to the excipient mixture. Processes for producing the inhalable powders according to the invention by grinding and micronising and by finally mixing the ingredients together are known from the prior art.

[0079] The inhalable powders according to the invention may be administered using inhalers known from the prior art. Inhalable powders according to the invention which contain one or more physiologically acceptable excipients in addition to 1 may be administered, for example, by means of inhalers which deliver a single dose from a supply using a measuring chamber as described in US 4570630, or by other means as described in DE 36 25 685. The inhalable powders according to the invention which contain 1 optionally in conjunction with a physiologically acceptable excipient may be administered, for example, using the inhaler known by the name Turbuhaler® or using inhalers as disclosed for example in EP 237507. Preferably, the inhalable powders according to the invention which contain physiologically acceptable excipient in addition to 1 are packed into capsules (to produce so-called inhalettes) which are used in inhalers as described, for example, in WO 94/28958.

[0080] Inhalation aerosols containing propellant gas may contain substance 1 dissolved in the propellant gas or in dispersed form. The propellant gases which may be used to prepare the inhalation aerosols according to the invention are known from the prior art. Suitable propellant gases are selected from among hydrocarbons such as n-propane, n-butane or isobutane and halohydrocarbons such as fluorinated derivatives of methane, ethane, propane, butane, cyclopropane or cyclobutane. The propellant gases mentioned above may be used on their own or in mixtures thereof. Particularly preferred propellant gases are halogenated alkane derivatives selected from TG11, TG12, TG134a (1,1,1,2-tetrafluoroethane) and TG227 (1,1,1,2,3,3,3-heptafluoropropane) and mixtures thereof, of which the propellant gases TG134a, TG227 and mixtures thereof are preferred.

[0081] The propellant-driven inhalation aerosols according to the invention may also contain other ingredients such as co-solvents, stabilisers, surfactants, antioxidants, lubricants and pH adjusters. All these ingredients are known in the art.

[0082] The inhalation aerosols containing propellant gas according to the invention may contain up to 5 wt.-% of active substance 1. Aerosols according to the invention contain, for example, 0.002 to 5 wt.-%, 0.01 to 3 wt.-%, 0.015 to 2 wt.-%, 0.1 to 2 wt.-%, 0.5 to 2 wt.-% or 0.5 to 1 wt.-% of active substance 1.

[0083] If the active substances 1 are present in dispersed form, the particles of active substance preferably have an average particle size of up to 10μm, preferably from 0.1 to 6μm, more preferably from 1 to 5μm.

[0084] The propellant-driven inhalation aerosols according to the invention mentioned above may be administered using inhalers known in the art (MDIs = metered dose inhalers). Suitable cartridges and methods of filling these cartridges with the inhalable aerosols containing propellant gas according to the invention are known from the prior art.

[0085] For example, and without restricting the scope of the invention thereto, in the use according to the invention tiotropium may be administered for instance in such amounts that each individual dose contains preferably 0.1 - 100μg. For example, and without restricting the scope of the invention thereto, 2.5μg, 5μg, 10μg, 18μg, 20μg, 36μg or 40μg of tiotropium (calculation based on cation) may be administered per single dose.

[0086] For example, and without restricting the scope of the invention thereto, in the use according to the invention glycopyrronium, preferably R,R-glycopyrronium may be administered for instance in such amounts that each individual dose contains preferably 1 - 300μg. For example, and without restricting the scope of the invention thereto, 25μg, 35μg, 45μg, 55μg, 65μg, 75μg, 85μg, 95μg, 105μg, 115μg, 125μg, 135μg, 145μg, 155μg, 165μg, 175μg, 185μg or 195μg of glycopyrronium (calculation based on cation) may be administered per single dose. Preferably the aforementioned doses are administered once, twice or three times per day, preferably twice or three times per day.

[0087] For example, and without restricting the scope of the invention thereto, in the use according to the invention compounds of formula 1a may be administered for instance in such amounts that each individual dose contains preferably 100 - 1800μg. For example, and without restricting the scope of the invention thereto, 100μg, 2005μg, 300μg, 400μg, 500μg, 600μg, 700μg, 800μg, 1000μg, 1100μg, 1200μg, 1300μg, 1400μg, 1500μg, 1600μg or 1700μg 1a' may be administered per single dose. Preferably the aforementioned doses are administered once or twice per day, preferably once per day.

[0088] For example, and without restricting the scope of the invention thereto, in the use according to the invention compounds of formula 1c may be administered for instance in such amounts that each individual dose contains preferably 1 - 500μg. For example, and without restricting the scope of the invention thereto, 25μg, 35μg, 45μg, 55μg, 65μg, 75μg, 85μg, 95μg, 105μg, 115μg, 125μg, 135μg, 145μg, 155μg, 165μg, 175μg, 185μg or 195μg of 1c' may be administered per single dose. Preferably the aforementioned doses are administered once or twice per day, preferably once per day.

[0089] For example, and without restricting the scope of the invention thereto, in the use according to the invention compounds of formula 1d may be administered for instance in such amounts that each individual dose contains preferably

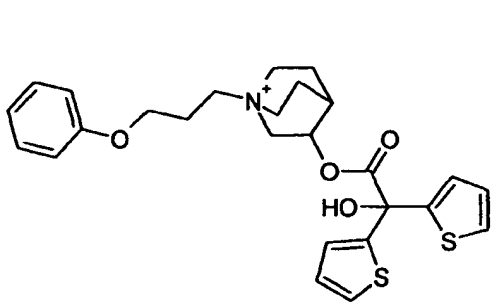
1 - 300μg. For example, and without restricting the scope of the invention thereto, 25μg, 35μg, 45μg, 55μg, 65μg, 75μg, 85μg, 95μg, 105μg, 115μg, 125μg, 135μg, 145μg, 155μg, 165μg, 175μg, 185μg or 195μg of 1d' may be administered per single dose. Preferably the aforementioned doses are administered once or twice per day, preferably once per day.

[0090] For example, and without restricting the scope of the invention thereto, in the use according to the invention compounds of formula 1e may be administered for instance in such amounts that each individual dose contains preferably 1 - 300μg. For example, and without restricting the scope of the invention thereto, 15μg, 25μg, 35μg, 45μg, 55μg, 65μg, 75μg, 85μg or 95μg of 1e' may be administered per single dose. Preferably the aforementioned doses are administered once or twice per day, preferably once per day.

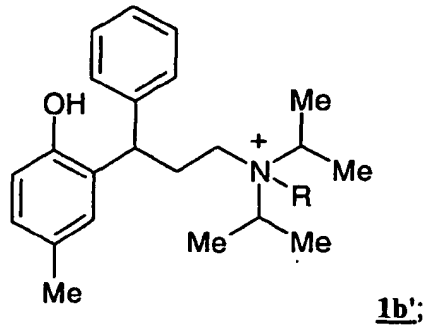
[0091] For example, and without restricting the scope of the invention thereto, in the use according to the invention compounds of formula 1f may be administered for instance in such amounts that each individual dose contains 1 - 300μg, preferably 5 - 250 μg, most preferably about 20 - 200μg. For example, and without restricting the scope of the invention thereto, 25μg, 35μg, 45μg, 55μg, 65μg, 75μg, 85μg, 95μg, 105μg, 115μg, 125μg, 135μg, 145μg, 155μg, 165μg, 175μg, 185μg or 195μg of 1f' may be administered per single dose. Preferably the aforementioned doses are administered once or twice per day, preferably once per day.

[0092] For example, and without restricting the scope of the invention thereto, in the use according to the invention compounds of formula 1g may be administered for instance in such amounts that each individual dose contains 1 - 250μg, preferably 5-150 μg, most preferably about 10 - 100μg. For example, and without restricting the scope of the invention thereto, 15μg, 25μg, 35μg, 45μg, 55μg, 65μg, 75μg, 85μg or 95μg of 1g' may be administered per single dose. Preferably the aforementioned doses are administered once or twice per day, preferably once per day.

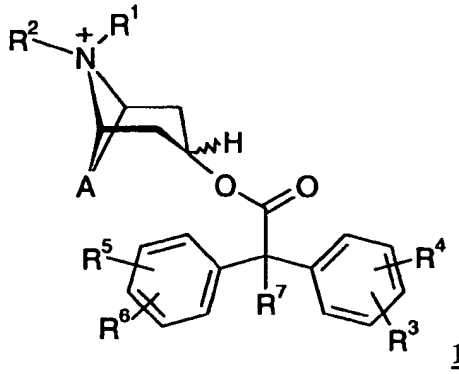
[0093] Within the scope of the present invention, any reference to the compounds 1' is to be regarded as a reference to the pharmacologically active cations contained in the salts 1. These are the cations tiotropium, glycopyrronium, trospium or the cations of the following formulae



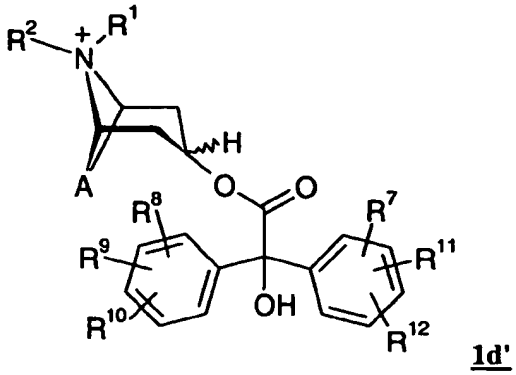
1a';



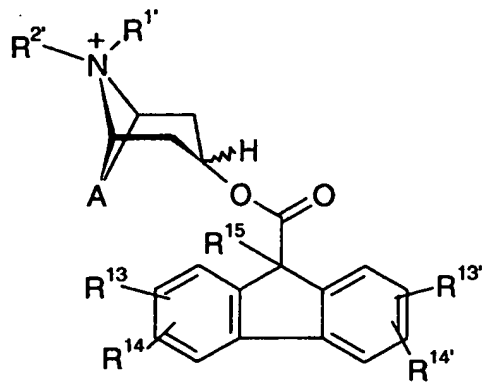
1b';



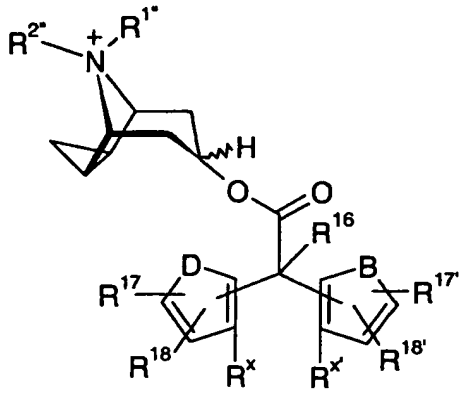
1c;



1d'

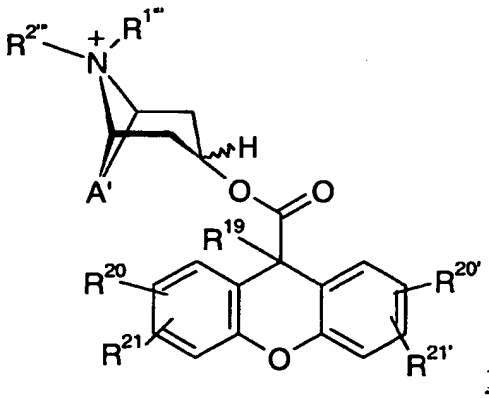


1e';



1f';

or



1g'.

[0094] The Examples which follow serve to illustrate the present invention in more detail without restricting the scope of the invention to the following embodiments by way of example.

Examples of Formulations

[0095] The following examples of formulations, which may be obtained analogously to methods known in the art, serve to illustrate the present invention more fully without restricting it to the contents of these examples.

Tablets:

[0096]

1)

Ingredients	mg per suppository
tiotropium bromide	3.3
dibasic calcium phosphate, anhydrous	33
maize starch dried	30
starch, soluble	2
silica colloidal	4

Table continued

Ingredients	mg per suppository
tartaric acid granule	0.5
stearic acid powder	0.5
povidone K25	0.505
sucrose refined	41.194
talc 405	23.671
acacia powdered	2.761
titanium dioxide	1.802
macrogel 6000	0.04
carnauba wax	0.018
beeswax white	0.009

2)

Ingredients	mg per suppository
scopine 2,2-diphenylpropionic acid ester methobromide	33
dibasic calcium phosphate, anhydrous	33
maize starch dried	30
starch, soluble	2
silica colloidal	4
tartaric acid granule	0.5
stearic acid powder	0.5
povidone K25	0.505
sucrose refined	41.194
talc 405	23.671
acacia powdered	2.761
titanium dioxide	1.802
macrogel 6000	0.04
carnauba wax	0.018
beeswax white	0.009

3)

Ingredients	mg per suppository
tropenol 2,2-diphenylpropionic acid ester methobromide	33
dibasic calcium phosphate, anhydrous	33
maize starch dried	30
starch, soluble	2
silica colloidal	4
tartaric acid granule	0.5

Table continued

Ingredients	mg per suppository
stearic acid powder	0.5
povidone K25	0.505
sucrose refined	41.194
talc 405	23.671
acacia powdered	2.761
titanium dioxide	1.802
macrogel 6000	0.04
carnauba wax	0.018
beeswax white	0.009

4)

Ingredients	mg per suppository
tropenol 2-fluoro-2,2-diphenylacetic acid ester methobromide	33
dibasic calcium phosphate, anhydrous	33
maize starch dried	30
starch, soluble	2
silica colloidal	4
tartaric acid granule	0.5
stearic acid powder	0.5
povidone K25	0.505
sucrose refined	41.194
talc 405	23.671
acacia powdered	2.761
titanium dioxide	1.802
macrogel 6000	0.04
carnauba wax	0.018
beeswax white	0.009

5)

Ingredients	mg per suppository
tropenol 9-fluoro-fluorene-9-carboxylate methobromide	10
dibasic calcium phosphate, anhydrous	33
maize starch dried	30
starch, soluble	2
silica colloidal	4
tartaric acid granule	0.5
stearic acid powder	0.5

Table continued

Ingredients	mg per suppository
povidone K25	0.505
sucrose refined	41.194
talc 405	23.671
acacia powdered	2.761
titanium dioxide	1.802
macrogel 6000	0.04
carnauba wax	0.018
beeswax white	0.009

6)

Ingredients	mg per suppository
scopine 9-fluoro-fluorene-9-carboxylate methobromide	10
dibasic calcium phosphate, anhydrous	33
maize starch dried	30
starch, soluble	2
silica colloidal	4
tartaric acid granule	0.5
stearic acid powder	0.5
povidone K25	0.505
sucrose refined	41.194
talc 405	23.671
acacia powdered	2.761
titanium dioxide	1.802
macrogel 6000	0.04
carnauba wax	0.018
beeswax white	0.009

7)

Ingredients	mg per suppository
tropenol 9-methyl-fluorene-9-carboxylate methobromide	10
dibasic calcium phosphate, anhydrous	33
maize starch dried	30
starch, soluble	2
silica colloidal	4
tartaric acid granule	0.5
stearic acid powder	0.5
povidone K25	0.505

Table continued

Ingredients	mg per suppository
sucrose refined	41.194
talc 405	23.671
acacia powdered	2.761
titanium dioxide	1.802
macrogel 6000	0.04
carnauba wax	0.018
beeswax white	0.009

8)

Ingredients	mg per suppository
scopine 9-methyl-fluorene-9-carboxylate methobromide	10
dibasic calcium phosphate, anhydrous	33
maize starch dried	30
starch, soluble	2
silica colloidal	4
tartaric acid granule	0.5
stearic acid powder	0.5
povidone K25	0.505
sucrose refined	41.194
talc 405	23.671
acacia powdered	2.761
titanium dioxide	1.802
macrogel 6000	0.04
carnauba wax	0.018
beeswax white	0.009

Ampoules:

[0097]

1)

Ingredients	content per ampoule
tiotropium bromide	0.17 mg
NaCl	6 mg
water purified	ad 1 ml

2)

Ingredients	content per ampoule
scopine 2,2-diphenylpropionic acid ester methobromide	1.7 mg

Table continued

Ingredients	content per ampoule
NaCl	6
water purified	ad 1 ml

3)

Ingredients	content per ampoule
tropenol 2,2-diphenylpropionic acid ester methobromide	1.7 mg
NaCl	6
water purified	ad 1 ml

4)

Ingredients	content per ampoule
scopine 4,4'-difluorobenzilic acid ester methobromide	1.7 mg
NaCl	6
water purified	ad 1 ml

5)

Ingredients	content per ampoule
tropenol 4,4'-difluorobenzilic acid ester methobromide	1.7 mg
NaCl	6
water purified	ad 1 ml

6)

Ingredients	content per ampoule
scopine 9-methyl-fluorene-9-carboxylate methobromide	0.5 mg
NaCl	6 mg
water purified	ad 1 ml

7)

Ingredients	content per ampoule
tropenol 9-methyl-fluorene-9-carboxylate methobromide	0.5 mg
NaCl	6 mg
water purified	ad 1 ml

8)

Ingredients	content per ampoule
cyclopropyltropine 2,2-diphenylpropionate methobromide	0.5 mg

Table continued

Ingredients	content per ampoule
Nacl	6 mg
water purified	ad 1 ml

9)

Ingredients	content per ampoule
cyclopropyltropine 9-hydroxy-xanthene-9-carboxylate methobromide	0.5 mg
NaCl	6 mg
water purified	ad 1 ml

10)

Ingredients	content per ampoule
cyclopropyltropine 9-methyl-xanthene-9-carboxylate methobromide	0.5 mg
NaCl	6 mg
water purified	ad 1 ml

Solution for injection:

[0098]

1)

Ingredients	content
tiotropium bromide	0.17 mg
methyl-4-hydroxybenzoate	18 mg
Propyl-4-hydroxybenzoate	2 mg
NaCl	60 mg
water purified	ad 10 ml

2)

Ingredients	content
tropenol 2,2-diphenylpropionic acid ester methobromide	1.7 mg
methyl-4-hydroxybenzoate	18 mg
Propyl-4-hydroxybenzoate	2 mg
NaCl	60 mg
water purified	ad 10 ml

3)

Ingredients	content
scopine 2,2-diphenylpropionic acid ester methobromide	1.7 mg

Table continued

Ingredients	content
methyl-4-hydroxybenzoate	18 mg
Propyl-4-hydroxybenzoate	2 mg
NaCl	60 mg
water purified	ad 10 ml

4)

Ingredients	content
scopine 2-fluoro-2,2-diphenylacetic acid ester methobromide	1.7 mg
methyl-4-hydroxybenzoate	18 mg
Propyl-4-hydroxybenzoate	2 mg
NaCl	60 mg
water purified	ad 10 ml

5)

Ingredients	content
tropenol 2-fluoro-2,2-diphenylacetic acid ester methobromide)	1.7 mg
methyl-4-hydroxybenzoate	18 mg
Propyl-4-hydroxybenzoate	2 mg
NaCl	60 mg
water purified	ad 10 ml

6)

Ingredients	content
tropenol 9-hydroxy-fluorene-9-carboxylate methobromide	0.5 mg
methyl-4-hydroxybenzoate	18 mg
Propyl-4-hydroxybenzoate	2 mg
NaCl	60 mg
water purified	ad 10 ml

7)

Ingredients	content
tropenol 9-fluoro-fluorene-9-carboxylate methobromide	0.5 mg
methyl-4-hydroxybenzoate	18 mg
Propyl-4-hydroxybenzoate	2 mg
NaCl	60 mg
water purified	ad 10 ml

8)

Ingredients	content
scopine 9-hydroxy-fluorene-9-carboxylate methobromide	0.5 mg
methyl-4-hydroxybenzoate	18 mg
Propyl-4-hydroxybenzoate	2 mg
NaCl	60 mg
water purified	ad 10 ml

9)

Ingredients	content
scopine 9-fluoro-fluorene-9-carboxylate methobromide	0.5 mg
methyl-4-hydroxybenzoate	18 mg
Propyl-4-hydroxybenzoate	2 mg
NaCl	60 mg
water purified	ad 10 ml

10)

Ingredients	content
tropenol 9-methyl-fluorene-9-carboxylate methobromide	0.5 mg
methyl-4-hydroxybenzoate	18 mg
Propyl-4-hydroxybenzoate	2 mg
NaCl	60 mg
water purified	ad 10 ml

11)

Ingredients	content
scopine 9-methyl-fluorene-9-carboxylate methobromide	0.5 mg
methyl-4-hydroxybenzoate	18 mg
Propyl-4-hydroxybenzoate	2 mg
NaCl	60 mg
water purified	ad 10 ml

Suppositories:

[0099]

1)

Ingredients I	mg per suppository
tiotropium bromide	3.3
water purified	10

Table continued

Ingredients I	mg per suppository
hard fat	1626.7
Total	1640

2)

Ingredients	mg per suppository
tropenol 2,2-diphenylpropionic acid ester methobromide	30
water purified	30
hard fat	1580
Total	1640

3)

Ingredients	mg per suppository
scopine 2,2-diphenylpropionic acid ester methobromide	30
water purified	30
hard fat	1580
Total	1640

4)

Ingredients	mg per suppository
tropenol 3,3',4,4'-tetrafluorobenzilic acid ester methobromide	10
water purified	10
hard fat	1620
Total	1640

5)

Ingredients	mg per suppository
scopine 3,3',4,4'-tetrafluorobenzilic acid ester methobromide)	10
water purified	10
hard fat	1620
Total	1640

6)

Ingredients	mg per suppository
tropenol 9-methyl-fluorene-9-carboxylate methobromide	10
water purified	10
hard fat	1620

Table continued

Ingredients	mg per suppository
Total	1640

7)

Ingredients	mg per suppository
scopine 9-methyl-fluorene-9-carboxylate methobromide	10
water purified	10
hard fat	1620
Total	1640

Claims

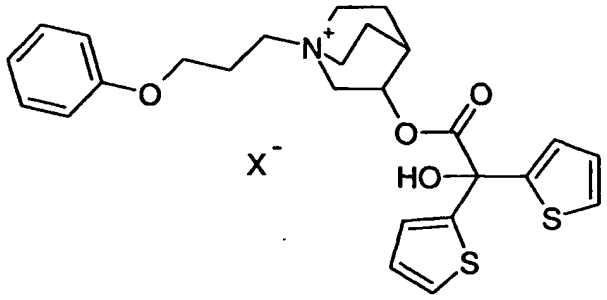
1. Use of one or more, preferably one long acting anticholinergic 1 for the preparation of a medicament for the treatment of urinary tract disorders.

2. Use according to claim 1 wherein the urinary tract disorder is selected from among urinary incontinence, urge urinary incontinence, stress urinary incontinence, mixed urinary incontinence, spasms of the urinary tract, urolithiasis, urinary tract cysts, urinary tract polyps, preparation for diagnostic and curative interventions in the urinary tract.

3. Use according to claim 1 or 2 wherein the long acting anticholinergic 1 is selected from among tiotropium salts, glycopyrronium salts and trospium salts, optionally in the form of its diasteromers, mixtures of its diasteromers, racemats or physiologically acceptable acid addition salts thereof, and optionally in form of the hydrates or solvates thereof.

4. Use according to claim 3 **characterised in that** the salts 1 contain as counter-ion (anion), chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate or p-toluenesulphonate.

5. Use according to claim 1 or 2 **characterised in that** 1 is a salt of formula 1a

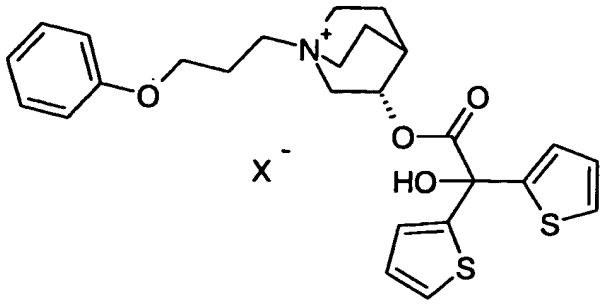


1a

wherein

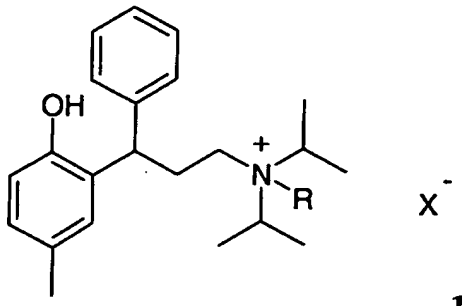
X^- denotes an anion with a single negative charge, preferably an anion selected from the group consisting of fluoride, chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate and p-toluenesulphonate.

6. Use according to claim 5 **characterised in that** 1 is present in form of the enantiomer formula 1a-en



1a-en.

7. Use according to claim 1 or 2 **characterised in that** 1 is a compound of formula **1b**

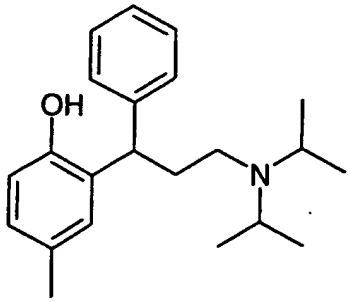


1b

wherein R is either methyl or ethyl and wherein

X^- denotes an anion with a single negative charge, preferably an anion selected from the group consisting of fluoride, chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate and p-toluenesulphonate.

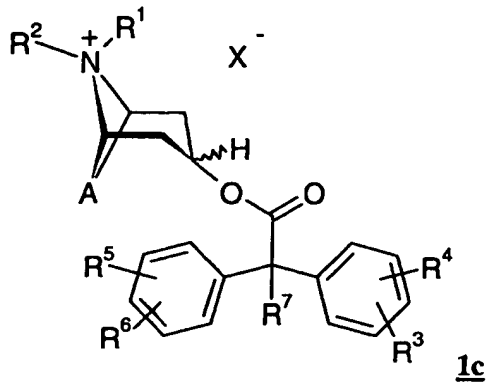
8. Use according to claim 1 or 2 **characterised in that** 1 is a compound of formula **1b-base**



1b-base.

9. Use according to claim 7 or 8, **characterised in that** **1b** or **1b-base** are present in form of its R-enantiomer.

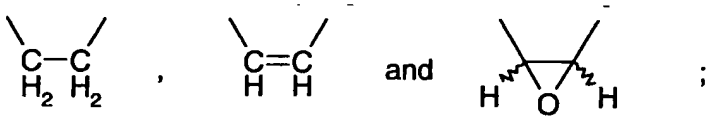
10. Use according to claim 1 or 2 **characterised in that** 1 is present in form of a compound of formula **1c**



1c

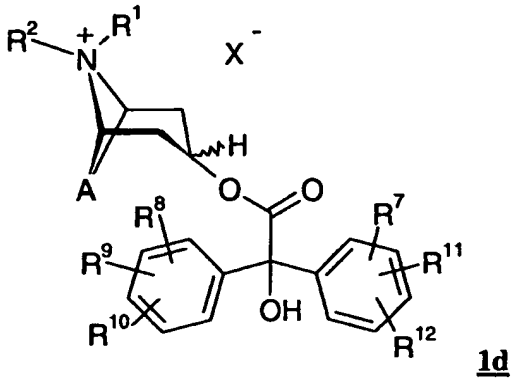
wherein

A denotes a double-bonded group selected from among



X⁻ denotes an anion with a single negative charge, preferably an anion selected from the group consisting of fluoride, chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate and p-toluenesulphonate;
R^1 and R^2 which may be identical or different denote a group selected from among methyl, ethyl, n-propyl and iso-propyl, which may optionally be substituted by hydroxy or fluorine, preferably unsubstituted methyl;
R^3, R^4, R^5 and R^6, which may be identical or different, denote hydrogen, methyl, ethyl, methyloxy, ethyloxy, hydroxy, fluorine, chlorine, bromine, CN, CF_3 or NO_2;
R^7 denotes hydrogen, methyl, ethyl, methyloxy, ethyloxy, $-CH_2$-F, $-CH_2-CH_2$-F, $-O-CH_2$-F, $-O-CH_2-CH_2$-F, $-CH_2$-OH, $-CH_2-CH_2$-OH, CF_3, $-CH_2$-OMe, $-CH_2-CH_2$-OMe, $-CH_2$-OEt, $-CH_2-CH_2$-OEt, -O-COMe, -O-COEt, $-O-COCF_3$, $-O-COCF_3$, fluorine, chlorine or bromine.

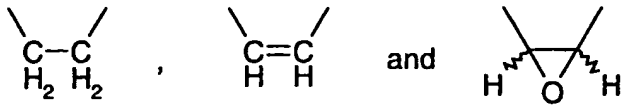
11. Use according to claim 1 or 2 **characterised in that** 1 is present in form of a compound of formula 1d



1d

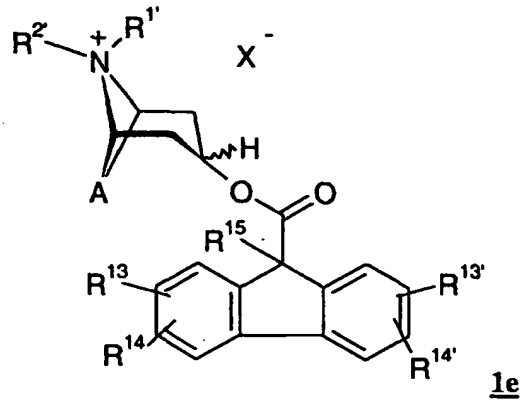
wherein

A denotes a double-bonded group selected from among



X - denotes an anion with a single negative charge, preferably an anion selected from the group consisting of fluoride, chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate and p-toluenesulphonate;
R^1 and R^2 which may be identical or different denote a group selected from among methyl, ethyl, n-propyl and iso-propyl, which may optionally be substituted by hydroxy or fluorine, preferably unsubstituted methyl;
R^7, R^8, R^9, R^{10}, R^{11} and R^{12}, which may be identical or different, denote hydrogen, methyl, ethyl, methyloxy, ethyloxy, hydroxy, fluorine, chlorine, bromine, CN, CF_3 or NO_2, with the proviso that at least one of the groups R^7, R^8, R^9, R^{10}, R^{11} and R^{12} is not hydrogen.

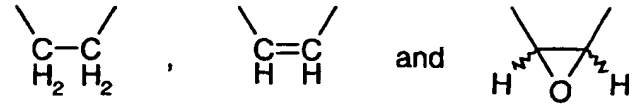
12. Use according to claim 1 or 2 **characterised in that** 1 is present in form of a compound of formula **1e**



1e

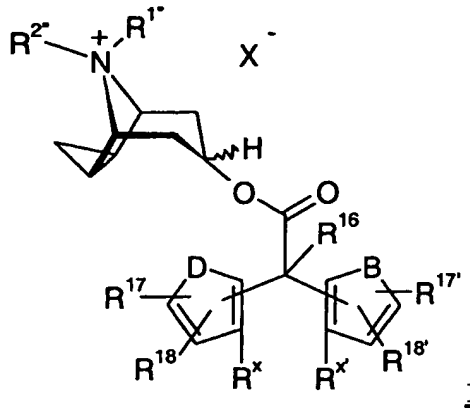
wherein

A denotes a double-bonded group selected from among



X^- denotes an anion with a single negative charge, preferably an anion selected from the group consisting of fluoride, chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate and p-toluenesulphonate;
R^{15} denotes hydrogen, hydroxy, methyl, ethyl, $-CF_3$, CBF_2 or fluorine;
$R^{1'}$ and $R^{2'}$ which may be identical or different denote C_1-C_5-alkyl which may optionally be substituted by C_3-C_6-cycloalkyl, hydroxy or halogen,
or
$R^{1'}$ and $R^{2'}$ together denote a -C_3-C_5-alkylene-bridge;
R^{13}, R^{14}, $R^{13'}$ and $R^{14'}$ which may be identical or different denote hydrogen, -C_1-C_4-alkyl, -C_1-C_4-alkyloxy, hydroxy, $-CF_3$, $-CHF_2$, CN, NO_2 or halogen.

13. Use according to claim 1 or 2 **characterised in that** 1 is present in form of a compound of formula **1f**



1f

wherein

X^- denotes an anion with a single negative charge, preferably an anion selected from the group consisting of fluoride, chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate and p-toluenesulphonate;

D and B which may be identical or different, preferably identical, denote -O, -S, -NH, $-CH_2$, -CH=CH, or -N(C_1-C_4-alkyl)-;

R^{16} denotes hydrogen, hydroxy, -C_1-C_4-alkyl, -C_1-C_4-alkyloxy, -C_1-C_4-alkylene-Halogen, -O-C_1-C_4-alkylene-halogen, -C_1-C_4-alkylene-OH, $-CF_3$, CHF_2, -C_1-C_4-alkylene-C_1-C_4-alkyloxy, -O-COC$_1$-C_4-alkyl, -O-COC$_1$-C_4-alkylene-halogen, -C_1-C_4-alkylene-C_3-C_6-cycloalkyl, -O-$COCF_3$ or halogen;

$R^{1''}$ and $R^{2''}$ which may be identical or different, denote -C_1-C_5-alkyl, which may optionally be substituted by -C_3-C_6-cycloalkyl, hydroxy or halogen,

or

$R^{1''}$ and $R^{2''}$ together denote a -C_3-C_5-alkylene bridge;

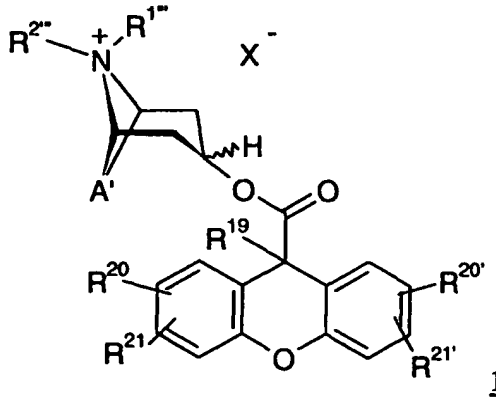
R^{17}, R^{18}, $R^{17'}$ and $R^{18'}$, which may be identical or different, denote hydrogen, C_1-C_4-alkyl, C_1-C_4-alkyloxy, hydroxy, $-CF_3$, $-CHF_2$, CN, NO_2 or halogen;

R^X and $R^{X'}$ which may be identical or different, denote hydrogen, C_1-C_4-alkyl, C_1-C_4-alkyloxy, hydroxy, $-CF_3$, $-CHF_2$, CN, NO_2 or halogen

or

R^X and $R^{X'}$ together denote a single bond or a bridging group selected from among the bridges -O, -S, -NH, $-CH_2$, $-CH_2$-CH_2-, -N(C_1-C_4-alkyl), -CH(C_1-C_4-alkyl)- and -C(C_1-C_4-alkyl)$_2$.

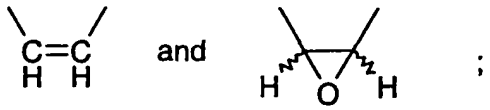
14. Use according to claim 1 or 2 **characterised in that** 1 is present in form of a compound of formula 1g



1g

wherein

X - denotes an anion with a single negative charge, preferably an anion selected from the group consisting of fluoride, chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate and p-toluenesulphonate;
A' denotes a double-bonded group selected from among



;

R^{19} denotes hydroxy, methyl, hydroxymethyl, ethyl, $-CF_3$, CHF_2 or fluorine;
$R^{1''}$ and R^2 which may be identical or different denote C_1-C_5-alkyl which may optionally be substituted by C_3-C_6-cycloalkyl, hydroxy or halogen,
or
$R^{1''}$ and $R^{2''}$ together denote a $-C_3$-C_5-alkylene-bridge;
R^{20}, R^{21}, $R^{20'}$ and $R^{21'}$ which may be identical or different denote hydrogen, $-C_1$-C_4-alkyl, $-C_1$-C_4-alkyloxy, hydroxy, $-CF_3$, $-CBF_2$, CN, NO_2 or halogen.

15. Use according to one of claims 1 to 14 wherein the long acting anticholinergic 1 is used for the preparation of a medicament suitable for oral, parenteral, buccal, nasal, vaginal, rectal, sublingual, topical or inhalative administration.

16. Dosage unit formulations for oral, parenteral, buccal, nasal, vaginal, rectal, sublingual or topical administration containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles in combination with a long acting anticholinergic as specified in one of claims 3 to 14.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 04 01 9003

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X Y	US 6 482 837 B1 (WOOD RONALD W) 19 November 2002 (2002-11-19) * column 6, line 3 - line 36 * * column 6, line 37 - line 45 * * column 6, line 46 - column 9, line 67 * * column 12, line 27 - line 60 * * column 13, line 17 - line 35 * * column 13, line 63 - column 14, line 1 * * column 34, line 10 - column 35, line 60 * -----	1-4, 10-16 5-7	A61K31/4439 A61K31/46 A61K31/14 A61P13/02
X	US 5 998 430 A (SCHAUPP ALBERT ET AL) 7 December 1999 (1999-12-07) * the whole document * -----	1-4,15, 16	
X	WO 2004/064789 A (WOOD RONALD W ; UNIV ROCHESTER (US)) 5 August 2004 (2004-08-05) * paragraph [0034] * * abstract * -----	1-4,15, 16	
X	WO 01/17480 A (ANDROSOLUTIONS INC) 15 March 2001 (2001-03-15) * page 10, paragraph 2 * * page 14, last paragraph * -----	1-4,15, 16	TECHNICAL FIELDS SEARCHED (Int.Cl.7) A61K
Y	SCHELFHOUT V.J. ET AL.: "Activity of LAS 34273, a new Long Acting Anticholinergic Agent, in COPD Patients"[Online] 19 May 2004 (2004-05-19), XP002298563 Retrieved from the Internet: URL:http://www.abstracts2view.com/atsall/search.php?query=Schelfhout&where[]=authors&search=do> [retrieved on 2004-09-28] * the whole document * -----	5,6	
	-/--		

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
Munich	30 September 2004	Giacobbe, S

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

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EUROPEAN SEARCH REPORT

Application Number
EP 04 01 9003

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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
Munich	30 September 2004	Giacobbe, S

CATEGORY OF CITED DOCUMENTS

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